525783

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 March 2004 (11.03.2004)

PCT

(10) International Publication Number
WO 2004/019947 A1

(51) International Patent Classification[7]: A61K 31/505, 31/439, 31/40, 31/351, 31/22, 31/404, 31/4418, 31/366, A61P 25/28

(21) International Application Number:
PCT/SE2003/001352

(22) International Filing Date:
1 September 2003 (01.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0202598-9 2 September 2002 (02.09.2002) SE

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **KEITH, Richard** [US/US]; AstraZeneca Wilmington, P.O. Box 15437, Wilmington, DE 19850-5437 (US).

(74) Agent: **ASTRAZENECA AB**; Global Intellectual Property, S-151 85 Södertälje (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/019947 A1

(54) Title: ALPHA-7 NICOTINIC RECEPTOR AGONISTS AND STATINS IN COMBINATION

(57) Abstract: Combinations of α7-nAChR agonists and statins, pharmaceutical compositions containing the same and methods of using the same useful for treatment or prophylaxis of neurological degenerative diseases.

Alpha-7 Nicotinic Receptor Agonists and Statins In Combination

Field of Invention:

This invention is concerned with the treatment of neurological degenerative diseases and particularly with the treatment of Alzheimer's disease.

Background

The etiology of Alzheimer's disease is complex and not entirely understood. Current hypotheses point to the overproduction of the amyloid peptide Aβ as a causative factor in the cognitive deficits and neurodegeneration associated with Alzheimer's disease (Selkoe, 2001; Walsh *et. al.*, 2002). In addition, epidemiological studies have shown that hypercholesterolemia is a risk factor for Alzheimer's disease (Jarvik *et. al.*, 1995; Notkola *et. al.*, 1998). Further, it has recently been shown that the administration of statins is associated with a decreased risk of Alzheimer's disease (Jick *et. al.*, 2000; Wolozin *et. al.*, 2000). Still further, another recent study has shown that the statin lovastatin reduced Aβ plasma levels in human subjects that had elevated plasma levels of low-density lipoprotein cholesterol (Buxbaum *et. al.*, 2002).

Alpha-7 nicotinic receptors (α7-nAChR) are ligand-gated ion channels that allow for the entry into cells of calcium and other monovalent cations (Dani, 2001). α7-nAChR have been shown to play an important role in regulating neurotransmitter release, hippocampal synaptic function, neuroprotection against a variety of insults, and cognition (Dani, 2001; Dahas-Bailador *et. al.*, 2000; Rezvani and Levin, 2001).

Recent studies imply an interaction between Aβ and α7-nAChR that may contribute to the pathophysiology of Alzheimer's disease. Aβ has been shown to potently inhibit α7-nAChR (Liu *et. al.*, 2001). It has been proposed that this inhibitory effect of Aβ on α7-nAChR function may contribute to cognitive deficits in Alzheimer's disease. Neurodegeneration induced by the activation of NMDA glutamatergic receptors is also enhanced in the presence of Aβ (Kihara *et. al.*, 2001). This Aβ induced neurodegeneration is inhibited by activation of α7-nAChR.

Background References:

Buxbaum JD, Cullen EI and Friedhoff LT: Pharmacological concentrations of the HMG-CoA reductase inhibitor lovastatin decrease the formation of the Alzheimer beta-amyloid peptide in vitro and in patients. *Frontiers in Bioscience* 7:a50-a59, 2002.

Dajas-Bailador FA, Lima PA and Wonnacott S: The α7 nicotinic receptor subtype mediates nicotine protection against NMDA excitotoxicity in primary hippocampal cultures through a Ca^{2+} dependent mechanism. *Neuropharmacology* 39:2799-2807, 2000.

Dani JA: Overview of nicotinic receptors and their roles in the central nervous system. *Biol Psychiatry* 49:166-174, 2001.

Kihara T, Shimohama S, Sawada H, Honda K, Nakamizo T, Shibasaki H, Toshiaki K, and Akaike A: α7 Nicotinic receptor transduces signals to phohphatidylinositol 3-kinase to block Aβ-amyloid-induced neurotoxicity. *J Biol Chem* 276:13541-13546, 1998.

Jick H, Zornberg GL, Jick SS, Seshadri S, and Drachman DA: Statins and the risk of dementia. *Lancet* 356:1627-1631, 2000.

Jarvik GP, Wijsman EM, Kukull WA, Schellenberg GD, Yu C and Larson EB: Interactions of apolipoprotein E genotype, total cholesterol, age, and sex in prediction of Alzheimer's disease. *Neurology* 45:1092-1096, 1995.

Liu Q, Kawai H and Berg DK: b-Amyloid peptide blocks the response of α7-containing nicotinic receptors on hippocampal neurons. *Proc Natl Acad Sci* 97:10197-10202, 2001.

Notkola IL, Sulkava R, Pekkanen J, Erkinjuntti T, Ehnholm C, Kivinen P, Tuomilehto J and Nissinen A: Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. *Neuroepidememiology* 17:14-20, 1998.

Rezvani AH and Levin ED: Cognitive effects of nicotine. *Biol Psychiatry* 49:258-267, 2001.

Selkoe, DJ: Alzheimer's disease: Genes, proteins, and therapy. *Physiological Reviews* 81:741-766, 2001.

Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, and Selkoe, DJ: Naturally secreted oligomers of amyloid β protein potently inhibit hippocampal long-term potentiation in vivo. *Nature* 416:535-539, 2002.

Wolozin B, Kellman W, Ruosseau P, Celesia GG, and Siegel G: Decreased prevalence of Alzheimer's disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. *Arch Neruol* 57:1439-1443, 2000.

Description of the Invention:

We have discovered that statins and α7-nAChR agonists in combination have the potential to alter the pathophysiology of Alzheimer's disease and symptoms. The different mechanisms by which statins and α7-nAChR agonists operate — statins by reducing the

formation of the neurotoxic substance Aβ and α7-nAChR agonists by blocking the cognitive impairing and neurotoxic effects of Aβ — imply that a statin and an α7-nAChR in combination will synergistically benefit patients suffering with neurological degenerative diseases and particularly patients suffering with Alzheimer's disease.

In one aspect the invention is a method for treating neurological degenerative diseases and particularly Alzheimer's disease comprising treatment with a combination comprising an α7-nAChR agonist and a statin.

A combination suitable for practicing the invention comprises a statin selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin sodium, simvastatin or rosuvastatin, or a pharmaceutically-acceptable salt thereof and an α7-nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,

(+)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,

(-)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,

spiro[1-azabicyclo[2.2.1]heptan-3,5'-oxazolidin-2'-one],

3'-methyl spiro-[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one],

spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

1'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline],

5'-(phenylcarboxamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-(phenylaminocarbonylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-(phenylsulfonylamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N,N-dimethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N,N-diethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N-ethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N-benzylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N-formamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-N-acetamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline],
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]quinoline],
5'-ethenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-(E)-(phenylethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-(4-morpholino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-(1-azetidinyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-(E)-(2-(4-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-(E)-(2-(2-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-(2-trimethylsilylethynyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-ethynylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-(2-furyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-(3-pyridyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-methylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5'carbonitrile],
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5'carboxamide],
5'-N'-(3-chlorophenyl)aminocarbonylminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-N'-(2-nitrophenyl)aminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
4'-methoxyspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
4'-phenylthiospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
4'-(N-2-aminoethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
4'-phenylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
4'-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

4'-(4-N-methylpiperazin-1-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

4'-chloro-spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine],

spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine],

spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide],

spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-6'-carbonitrile],

6'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine],

6'-fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine],

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-chlorophenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide),

N-(1-aza-bicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide); *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide),

(R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)[5-(4-chlorophenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide),

(S)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);

(S)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),

(S)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),

(S)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide),

(R)-*N*-(1-aza-bicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ,

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide), or

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide), or a pharmaceutically-acceptable salt thereof.

In general, it is contemplated that any statin when used in combination with any alpha-7-nAChR agonist will be useful in practicing the present invention.

Alpha-7-nAChR agonists contemplated to be useful in the present invention are described in international publications WO9606098, WO9730998, WO 9903859,

WO9956745, WO0042044, WO0129034, WO0160821, WO0132622, WO0136417, WO0132619, WO0132620, WO0136417, WO0244176, WO0220521, WO0216358, WO0216357, WO0216356, WO0216355, WO0215662 and WO0217358 and in publications EP1219622, EP1184383, EP1184384, EP1184385, JP200203084. Statins contemplated to be useful in the present inventions are atorvastatin calcium (Lipitor), cerivastatin sodium (Baycol), fluvastatin sodium (Lescol), lovastatin (Mevacor), pravastatin sodium (Pravachol), simvastatin (Zocor) and rosuvastatin (Crestor).

In another aspect the invention is a pharmaceutical composition comprising a combination of an α7-nAChR agonist and a statin as described herein together with a pharmaceutically-acceptable diluent or excipient.

In another aspect the present invention comprises providing neuroprotection or analgesia in a method of treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease which method comprises administering a therapeutically effective amount of a combination as defined in Claim 1 to a patient.

In a particular aspect the method of the invention is a method for the treatment or prophylaxis of Alzheimer's disease.

A further aspect of the invention is the use of a combination of an α7-nAChR agonist and a statin as described herein in the preparation of a medicament for providing neuroprotection or analgesia in the treatment of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease.

In a particular aspect the use of a combination of an α7-nAChR agonist and a statin as described herein is in the preparation of a medicament for the treatment or prophylaxis of Alzheimer's disease.

A particular combination for use in the present invention comprises rosuvastatin or a pharmaceutically-acceptable salt thereof and an α7-nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one, *N*-(1-azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof.

A particular pharmaceutical composition for use in the present invention comprises rosuvastatin or a pharmaceutically-acceptable salt thereof and an α7-nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one, *N*-(1-azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

A particular method of the present invention is the provision of neuroprotection or analgesia for the treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease which method comprises administering a therapeutically effective amount of a combination of rosuvastatin or a pharmaceutically-acceptable salt thereof and an α7-nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one, *N*-(1-azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof to a patient. In particular the method is useful for the treatment or prophylaxis Alzheimer's disease.

A particular embodiment of the invention is the use of a combination rosuvastatin or a pharmaceutically-acceptable salt thereof and an α7-nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one, *N*-(1-azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof in the preparation of a medicament providing neuroprotection or analgesia for the treatment of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease. In particular the invention comprises the use of such a combination in the preparation of a medicament for the treatment of Alzheimer's disease.

Statins are compounds that inhibit HMG-CoA reductase, a rate-limiting enzyme in the biosynthetic pathway to cholesterol. Statins are conventionally used to reduce plasma levels of cholesterol in patients with cardiovascular disease but can also reduce Aβ serum levels in patients. Alpha-7-nAChR agonists beneficially activate α7-nACh receptors and are useful for treating cognitive deficits and in the treatment of a range of disorders involving reduced cholinergic function such as Alzheimer's disease, cognitive or attention disorders, anxiety,

depression, smoking cessation, neuroprotection, schizophrenia, analgesia, Tourette's syndrome, and Parkinson's disease. Accordingly, the hypothetical basis of the present invention lies in the realization that statins, by reducing the formation of Aβ, may be particularly effective in combination with α7-nAChR agonists, which ameliorate cognitive deficits and inhibit neurodegeneration induced by Aβ, in the treatment of Alzheimer's disease. Therefore, the treatment of Alzheimer's disease with a combination of a statin and an α7-nAChR agonist will result in enhanced efficacy over either type of agent if administered alone.

Experimental:

Assessment of the efficacy of a statin and an α7-nAChR agonist in combination in animal models is not straightforward. Existing experimental models of Alzhiemer's disease include transgenic mice, which over express Aβ, and animals with surgically generated fimbria-fornix lesions. These models and the uses to which they may be put are known, understood and appreciated by those of skill in the relevant art. Transgenic mice which over express Aβ exhibit some of the clinical manifestations of Alzheimer's disease, *e.g.*, plaque deposition and, in some cases, cognitive deficits, but neurodegeneration is not observed. Animals with fimbria-fornix lesions have cognitive and learning deficits and have been used to assess potential approaches to treat neurodegeneration. No single experimental model exhibits the entire pathophysiological complex of Alzheimer's disease. However, to the extent that these models do mimic the pathophysiology of Alzheimer's disease they may be used to assess the effect of a statin and an α7-nAChR agonist in combination.

Claims:

1. A combination comprising:

a statin selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin sodium, simvastatin or rosuvastatin, or a pharmaceutically-acceptable salt thereof and

an α7-nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,

(+)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,

(-)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,

spiro[1-azabicyclo[2.2.1]heptan-3,5'-oxazolidin-2'-one],

3'-methyl spiro-[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one],

spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

1'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline],

5'-(phenylcarboxamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-(phenylaminocarbonylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-(phenylsulfonylamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N,N-dimethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N,N-diethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N-ethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N-benzylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N-formamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N-acetamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline],

spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]quinoline],

5'-ethenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-(E)-(phenylethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-(4-morpholino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-(1-azetidinyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-(E)-(2-(4-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-(E)-(2-(2-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-(2-trimethylsilylethynyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-ethynylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-(2-furyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-(3-pyridyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-methylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5'carbonitrile],

spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5'carboxamide],

5'-N'-(3-chlorophenyl)aminocarbonylminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

5'-N'-(2-nitrophenyl)aminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

4'-methoxyspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

4'-phenylthiospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

4'-(N-2-aminoethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

4'-phenylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

4'-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

4'-(4-N-methylpiperazin-1-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

4'-chloro-spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine],

spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine],

spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide],

spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-6'-carbonitrile],
6'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine],
6'-fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine],
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-chlorophenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide),

N-(1-aza-bicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ,

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*,*N*-dimethylamino)phenyl)furan-2-carboxamide),

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide); *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)[5-(4-chlorophenyl)furan-2-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*,*N*-dimethylamino)phenyl)thiophene-2-carboxamide).

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide),
(S)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);
(S)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),
(S)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),
(S)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide),
(R)-*N*-(1-aza-bicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ,
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide), or
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide), or a pharmaceutically-acceptable salt thereof.

2. A pharmaceutical composition comprising a combination according to Claim 1 together with a pharmaceutically acceptable diluent or carrier.

3. A method providing neuroprotection or analgesia for the treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease which method comprises

administering a therapeutically effective amount of a combination as defined in Claim 1 to a patient.

4. The method according to Claim 3, for treatment or prophylaxis of Alzheimer's disease.

5. The use of a combination according to Claim 1 in the preparation of a medicament providing neuroprotection or analgesia for the treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease.

6. The use of a combination according to Claim 5, in the preparation of a medicament for the treatment or prophylaxis of Alzheimer's disease.

7. A combination according to Claim 1, wherein said statin is rosuvastatin or a pharmaceutically-acceptable salt thereof and

said α7-nAChR agonist is selected from:

spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one;

N-(1-Azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or

(2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof.

8. A pharmaceutical composition comprising a combination according to Claim 7 together with a pharmaceutically acceptable diluent or carrier.

9. A method providing neuroprotection or analgesia for treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease which method comprises administering a therapeutically effective amount of a combination as defined in Claim 7 to a patient.

10. The method according to Claim 9, for treatment or prophylaxis of Alzheimer's disease.

11. The use of a combination according to Claim 7, in the preparation of a medicament providing neuroprotection or analgesia for the treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease.

12. The use of a combination according to Claim 11, in the preparation of a medicament for the treatment or prophylaxis of Alzheimer's disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01352

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/505, A61K 31/439, A61K 31/40, A61K 31/351, A61K 31/22, A61K 31/404, A61K 31/4418, A61K 31/366, A61P 25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, EPO-INTERNAL, CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Lancet, Volume 356, 11 November 2000, H Jick et al: "Statins and the risk of dementia", page 1627 - page 1631 --	1-12
Y	Frontiers in Bioscience, Volume 7, 1 April2002, Joseph D. Buxbaum et al: "Pharmacological concentrations of the HMG-COA reductase inhibitor lovastatin decrease the formation of the alzheimer Beta-amyloid peptide in vitro and in patients", page 50 - page 59 --	1-12
Y	WO 0132620 A1 (ASTRAZENECA AB), 10 May 2001 (10.05.01) --	1-12

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 December 2003	04 -12- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anna Sjölund/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01352

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6110914 A (EIFION PHILLIPS ET AL), 29 August 2000 (29.08.00) --	1-12
Y	WO 0042044 A1 (ASTRAZENECA AB), 20 July 2000 (20.07.00) --	1-12
Y	WO 9606098 A1 (ASTRA AKTIEBOLAG), 29 February 1996 (29.02.96) --	1-12
Y	US 2002042429 A (JASON K. MYERS ET AL), 11 April 2002 (11.04.02) --	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01352

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 3-4,9-10
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 3-4, 9-10 relates to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/09/03

International application No. PCT/SE 03/01352

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0132620 A1	10/05/01	AU 1745501 A	14/05/01
		EP 1230217 A	14/08/02
		JP 2003513072 T	08/04/03
		SE 9903996 D	00/00/00
US 6110914 A	29/08/00	AT 225792 T	15/10/02
		AU 739022 B	04/10/01
		AU 8367998 A	10/02/99
		BR 9810924 A	15/08/00
		CN 1117755 B	13/08/03
		CN 1270592 T	18/10/00
		DE 69808631 D,T	12/06/03
		DK 996622 T	30/12/02
		EE 200000031 A	16/10/00
		EP 0996622 A,B	03/05/00
		SE 0996622 T3	
		EP 1213291 A	12/06/02
		ES 2185185 T	16/04/03
		HU 0003844 A	30/07/01
		IL 134086 D	00/00/00
		JP 2001510194 T	31/07/01
		NO 20000226 A	14/03/00
		NZ 502298 A	01/02/02
		PL 338259 A	09/10/00
		PT 996622 T	31/01/03
		RU 2202553 C	20/04/03
		SE 9702746 D	00/00/00
		SI 996622 T	00/00/00
		SK 183599 A	14/08/00
		TR 200000129 T	00/00/00
		TW 515799 B	00/00/00
		US 6369224 B	09/04/02
		US 2003166935 A	04/09/03
		WO 9903859 A	28/01/99
		ZA 9805995 A	03/08/99
		SE 9800977 D	00/00/00
		WO 9961990 A	02/12/99
		AU 1580799 A	16/06/99
		SE 513538 C	25/09/00
		SE 9801364 A	03/06/99
		WO 9928805 A	10/06/99

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/09/03

International application No.
PCT/SE 03/01352

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0042044 A1	20/07/00	AT 240960 T	15/06/03
		AU 2334300 A	01/08/00
		BR 9916906 A	30/10/01
		CA 2359990 A	20/07/00
		CN 1337964 T	27/02/02
		CZ 20012554 A	16/01/02
		DE 69902753 D,T	15/05/03
		DE 69908185 D	00/00/00
		DK 1147114 T	15/09/03
		EE 200100370 A	15/10/02
		EP 1054754 A,B	29/11/00
		EP 1147114 A,B	24/10/01
		SE 1147114 T3	
		HU 0200513 A	29/06/02
		IL 144266 D	00/00/00
		JP 2002502715 T	29/01/02
		JP 2002534525 T	15/10/02
		NO 20013478 A	14/09/01
		NZ 512733 A	29/08/03
		SE 9900100 D	00/00/00
		SK 9932001 A	04/04/02
		TR 200102042 T	00/00/00
		US 6527060 B	04/03/03
		US 2003149065 A	07/08/03
		ZA 200105527 A	04/10/02

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/09/03

International application No.
PCT/SE 03/01352

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9606098 A1	29/02/96	AT 192157 T	15/05/00
		AU 690735 B	30/04/98
		AU 3401895 A	14/03/96
		BR 9508751 A	12/08/97
		CN 1056846 B	27/09/00
		CN 1099419 B	22/01/03
		CN 1159808 A	17/09/97
		CN 1284505 A	21/02/01
		CZ 289512 B	13/02/02
		CZ 9700392 A	17/12/97
		DE 69516524 D,T	18/01/01
		DK 777671 T	24/07/00
		EE 3399 B	16/04/01
		EE 9700039 A	15/08/97
		EP 0777671 A,B	11/06/97
		SE 0777671 T3	
		ES 2145922 T	16/07/00
		FI 970762 A	24/02/97
		GB 9417084 D	00/00/00
		GR 3033878 T	30/11/00
		HK 1010370 A	00/00/00
		HU 77352 A	30/03/98
		IL 115039 A	26/08/01
		JP 10504561 T	06/05/98
		NO 307707 B	15/05/00
		NO 970800 A	21/02/97
		NZ 292289 A	27/05/98
		PL 183933 B	30/08/02
		PL 318760 A	07/07/97
		PT 777671 T	31/08/00
		RU 2148058 C	27/04/00
		SK 21697 A	10/09/97
		SK 282366 B	07/01/02
		TR 960167 A	00/00/00
		TW 397837 B	00/00/00
		US 5902814 A	11/05/99
		US 6051581 A	18/04/00
		ZA 9507122 A	18/04/96
		GB 9504627 D	00/00/00
US 2002042429 A	11/04/02	US 6500840 B	31/12/02
		AU 8287501 A	04/03/02
		AU 8291001 A	04/03/02
		AU 8464601 A	04/03/02
		EP 1311505 A	21/05/03
		US 6492385 B	10/12/02
		US 6599916 B	29/07/03
		US 2002042428 A	11/04/02
		US 2002091135 A	11/07/02
		WO 0215662 A	28/02/02
		WO 0216355 A	28/02/02
		WO 0217358 A	28/02/02

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☑ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.